DOSSAGE OF LIGNOCaine IN EPIDURAL BLOCK IN RELATION TO TOXICITY

BY

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SUMMARY

The plasma concentrations reached following the epidural injection of 200, 400, 500, 600 and 700 mg of lignocaine have been determined. From these results, a linear relationship between dosage and plasma concentration was established. Plasma concentrations following rapid injection (400 mg in 15 seconds) were determined and found to be slightly higher than slower (60 seconds) injection. Statistical analysis of data has allowed a preliminary evaluation of the effects of weight and age upon the plasma concentrations of lignocaine. Recommendations on the dosage of lignocaine in epidural block in regard to toxicity are made, and the effects of the various factors affecting the absorption and elimination of local anaesthetic agents are assessed.

Epidural block often requires a relatively large quantity of local analgesic drug and, with lignocaine, the amount may exceed the maximum dose generally recommended. The Scandinavian Pharmacopoeia Council (1957) laid down that the maximum dose for lignocaine should be 200 mg plain or 500 mg with adrenaline, and these figures have been widely accepted (Deacock and Simpson, 1964). Recommendations of this type, however, are only meaningful if the conditions applying to the administration are closely defined. Thus, in some circumstances, 200 mg of plain lignocaine could be quite inadequate, while in others, 500 mg with adrenaline might well be dangerous.

The systemic toxicity of a local anaesthetic depends upon the level of the drug reached in the blood following absorption from the site of injection. Measurement of the plasma concentration is, therefore, of great value in determining the relative importance of the various factors which may affect toxicity. Among such factors the most important are:

(a) dose of local analgesic;
(b) site of injection;
(c) drug used;
(d) concentration of solution;
(e) addition of adrenaline;
(f) speed of injection;
(g) body weight and age of patient;
(h) rate of elimination.

In addition, the effect of a concomitant general anaesthetic must be considered as this will raise the threshold of plasma concentration at which toxic manifestations become apparent (Bromage and Robson, 1961).

Previous work has shown that epidural block gives significantly lower plasma levels than intercostal block. In addition, the effects of adding adrenaline, altering the concentration of solution, and changing the drug injected have been described (Braid and Scott, 1965). Those studies were carried out using the same dose of local analgesic (400 mg). Before the results can be extrapolated to other dosages, it is necessary to establish that a linear relationship between dosage and plasma level exists. Considering the complex way in which local analgesics are absorbed and eliminated, it cannot be assumed, for example, that doubling the dose will double the plasma concentrations. The present work was undertaken to determine the effect of various doses upon the plasma levels found during epidural block. In addition, the effect of rapid injection was observed and, from all the data so far obtained, an attempt has been made to assess the importance of body weight and age.

Thus, in relation to epidural block with lignocaine, all the factors (with the exception of rate of elimination) which the administrator can either control or make allowances for, have been investigated and their relative importance assessed.
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METHOD

Patients. Sixty-five patients were investigated. All were adult females undergoing major gynaecological surgery and all received a light general anaesthetic in addition to an epidural block. No form of selection was used in allocating patients to the various dosage groups, with the exception that the very old and infirm were not included in the highest dosage group.

Drug. The analgesic solution employed in every patient was 2 per cent plain lignocaine.

Epidural block. The epidural blocks were performed in the second or third lumbar intervertebral space using the loss-of-resistance technique, a syringe being filled with sterile saline to identify the space. The space identified, the chosen solution was injected.

Rate of injection. In the majority of cases the injection was made at a rate of 20 ml/min, but in one group of 12 patients receiving 20 ml of solution (400 mg), the injection was made over 15 seconds.

Dosage. The dose of lignocaine was varied from 200 mg to 700 mg, i.e. from 10 ml of solution to 35 ml.

The number of patients in each group, the dose of lignocaine and the period of injection are given in table I.

General anaesthesia. A light general anaesthetic, consisting of thiopentone (400 mg) followed by nitrous oxide/oxygen, was given to all patients. In most cases this was given subsequent to the epidural block, but in the series receiving rapid injection, it preceded the block to avoid any discomfort arising from the fast instillation of local anaesthetic into the epidural space.

Sampling and estimations. The method of sampling, the analytic technique and its accuracy have been described in a previous paper (Braid and Scott, 1965).

TREATMENT OF RESULTS

By taking six samples from each patient it is possible to plot a curve of the rise and fall of the plasma concentration following injection of the drug. To obtain a representative curve for a group of subjects it is desirable to calculate mean

<table>
<thead>
<tr>
<th>Dose (mg) and No. of patients (n)</th>
<th>Plasma concentration in µg/ml with standard deviation of mean</th>
</tr>
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<tbody>
<tr>
<td>200 (n=11)</td>
<td>5 min</td>
</tr>
<tr>
<td></td>
<td>2.21</td>
</tr>
<tr>
<td></td>
<td>± 0.18</td>
</tr>
<tr>
<td>400 (n=15)</td>
<td>2.62</td>
</tr>
<tr>
<td></td>
<td>± 0.32</td>
</tr>
<tr>
<td>500 (n=8)</td>
<td>4.44</td>
</tr>
<tr>
<td></td>
<td>± 0.43</td>
</tr>
<tr>
<td>600 (n=10)</td>
<td>4.35</td>
</tr>
<tr>
<td></td>
<td>± 0.40</td>
</tr>
<tr>
<td>700 (n=9)</td>
<td>4.20</td>
</tr>
<tr>
<td></td>
<td>± 0.29</td>
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</tbody>
</table>

Table I

Number of patients in each group, the corresponding dose of lignocaine and period of injection. The series of 15 patients receiving 400 mg lignocaine over 60 seconds has been reported before (Braid and Scott, 1965).

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Dose (mg)</th>
<th>Vol. of 2% sol. (ml)</th>
<th>Period of injection (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>200</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>15</td>
<td>400</td>
<td>20</td>
<td>60</td>
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<tr>
<td>12</td>
<td>400</td>
<td>20</td>
<td>15</td>
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<tr>
<td>8</td>
<td>500</td>
<td>25</td>
<td>75</td>
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<tr>
<td>10</td>
<td>600</td>
<td>30</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>700</td>
<td>35</td>
<td>105</td>
</tr>
</tbody>
</table>
values. The standard deviations are also given for each mean concentration. It is also of value in the comparison of the various series to compare the maximum mean concentrations with no respect to time of sampling. Such values are also given in the results.

RESULTS

Alteration of dose. The results from the five groups in which the dose of lignocaine was increased from 200 mg to 700 mg are given in table II and presented graphically in figure 1. In figure 2, the maximum values have been plotted against the dose of lignocaine and the regression line shown. These results indicate that a linear relationship between dosage and plasma concentrations exists.

Rate of injection. In a series of 12 patients, the epidural injection of 20 ml of 2 per cent plain solution (400 mg) was made in 15 seconds. The relevant results are given in table III and presented graphically in figure 3. For comparison, the results of epidural injection of the same solution in another series of patients over a period of 60 seconds are given.

It will be seen that rapid injection does give slightly higher levels than slow injection, although the difference is only statistically significant at two of the time intervals.

Body weight and age. From our accumulated data, we have attempted to assess the importance of body weight and age upon the plasma concentration. The largest group receiving the same dosage was that receiving 400 mg of plain lignocaine. Scatter diagrams of patients receiving this dosage (figs. 4 and 5) show that, in spite of wide

<table>
<thead>
<tr>
<th>Table III</th>
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<tr>
<td>Comparison of plasma concentrations following epidural injection of 400 mg of lignocaine given over 60 seconds and over 15 seconds. The statistical analysis was based on the Student &quot;t&quot; test.</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Speed of injection and No. of patients (n)</th>
<th>Plasma concentration in µg/ml with standard deviation of mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 sec (n=15)</td>
<td>2.62 ± 0.32</td>
</tr>
<tr>
<td>15 sec (n=12)</td>
<td>2.23 ± 0.47</td>
</tr>
<tr>
<td>&quot;t&quot; value</td>
<td>0.71</td>
</tr>
<tr>
<td>Level of significance (P)</td>
<td>NS</td>
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</tbody>
</table>

NS = Not significant.
variation in both weight and age, neither factor seemed to have more than a slight effect upon the plasma concentration. Analysis of all groups indicates that the maximum plasma concentration has an inverse relationship with body weight and a direct relationship with age, but both relationships are of a minor order compared with that between plasma concentration and dosage. Further work is required before this problem is finally resolved, but from this preliminary examination of our results, it would appear that body weight and age have only slight effects upon the plasma concentrations of lignocaine in adult females.

Maximum plasma concentrations of lignocaine in all patients plotted against dosage. The regression line and its formula are shown. The correlation coefficient $r=0.84$ is highly significant ($t=13.1, P<0.001$).

![Regression Line: $y=1.02+0.0095x$](image)

*Fig. 2*

Scatter diagram relating maximum plasma concentration in all patients receiving 400 mg of lignocaine and body weight.

![Plasma concentrations of lignocaine following rapid epidural injection (15 sec) of 400 mg compared with injection over 60 sec.](image)

*Fig. 3*
DISCUSSION

Dosage in lumbar epidural block is usually determined by the extent of the required area of analgesia. If a high spread is required (for example, for induced hypotension), then doses of lignocaine up to 600 mg may be required. It is important, therefore, that the possibility of generalized toxicity be borne in mind.

Foldes and colleagues (1960) found that, in conscious patients, systemic toxicity occurred with lignocaine when the plasma level reached 5 \( \mu \text{g/ml} \). This was confirmed by Englesson and associates (1962) who also found a similar result with prilocaine. Considerably higher plasma concentrations than this may be necessary for toxic effects to become serious.

Bromage and Robson (1961) found that, when lignocaine was given to anaesthetized patients, overt toxicity was not seen until the plasma level reached 10 \( \mu \text{g/ml} \) and then it usually took the form of cardiovascular depression. Whether this is a true elevation of the toxic threshold, or is due to suppression of the central nervous excitation, it is not possible to say, but there is little doubt that the dosage of lignocaine can be increased without apparent harm to the patient if general anaesthesia is used. From our results, it would appear that a dosage of 400 mg would be unlikely to give rise to more than slight symptoms of toxicity in conscious patients, and we would consider this to be the maximum dose in these circumstances. This is borne out by the experience of Bonica and associates (1957), who reported 3,637 epidural blocks in conscious patients. They found a low incidence of toxic effects, which were mild in 212 (6 per cent) and severe (with convulsions) in only 8 (0.2 per cent) using lignocaine with adrenaline in doses of up to 500 mg. In spite of the rarity of serious toxicity in this dose range, the anaesthetist must still be aware of the possibility and be able to deal with it efficiently and expeditiously.

The administration of concomitant general anaesthesia will allow a further increase in dosage, plasma levels of 10 \( \mu \text{g/ml} \) being unlikely to occur with dosage less than 600 mg of plain lignocaine. In our experience of over 2,000 epidural blocks, combined with general anaesthesia, overt toxicity has never been seen although the dosage has been in the range of 400–600 mg of plain lignocaine. The use of larger doses than 600 mg we would consider to be quite unnecessary in clinical practice.

That we were unable to show a much closer relationship between body weight and plasma concentrations may be due to the fact that all our patients were adult females. Such patients differ from each other in body weight more in regard to the degree of obesity than in lean body mass. As far as the absorption, distribution and elimination of these drugs are concerned, the lean
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Adrenaline does increase the intensity of block and lengthens its duration (Bromage et al., 1964), and it is of value on these grounds alone, although some authors have incriminated it as an aetiological factor in the production of anterior spinal artery thrombosis (Davies, Solomon and Levene, 1958; Catterberg and Insauti, 1964).

Speed of injection. This appears to be of some importance in relation to toxicity, but in any case, injection should not be too rapid, otherwise the cerebrospinal fluid pressure may increase and give rise to discomfort in conscious patients. One ml of solution every 2–3 seconds is well tolerated by most patients.

Body weight and age. In adult patients our work suggests that little account should be taken of body weight in calculating dosage. More elderly people are less likely to tolerate high plasma levels which may occur, and as it is well established that the spread of analgesic solution in the epidural space is enhanced with increasing age (Bromage, 1962), high dosage is both unnecessary and undesirable.

ACKNOWLEDGEMENTS

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REFERENCES


body mass is probably of much greater importance than total body weight, for it is unlikely that the acquisition of several kilograms of fat would appreciably reduce the likelihood of toxicity from local anaesthetics. Indeed, it could well be that the thin, nervous woman, with a higher metabolic rate, could attain lower plasma levels than her slow, obese sister. It would seem important to differentiate between large patients and obese ones. This, of course, is much easier in children than in adults, and dosage on a mg/kg basis is probably only valid in the former.

Because the dose/plasma concentration relationship is linear it is possible to extrapolate the results of earlier work on other factors affecting the absorption of lignocaine. Thus, all the main factors which can be controlled by the administrator in epidural block have now been assessed and may be summarized as follows:

Dosage. Using plain lignocaine, a dose of 400 mg should not be exceeded in conscious patients, but if general anaesthesia is given this may be increased to 600 mg.

Drug used. Plain lignocaine gives plasma levels 46–54 per cent above those of prilocaine (Braid and Scott, 1965) and if the latter drug is used, dosage may be increased to 600 mg for the conscious patient.

Concentration of solution. In concentrations of up to 2 per cent, this factor is of no importance in epidural block (Braid and Scott, 1965).

Addition of adrenaline. Adrenaline lowers the plasma level of lignocaine by 25 per cent if used in a 1-in-80,000 concentration, and by 18 per cent with a 1-in-200,000 concentration (Braid and Scott, 1965). Adrenaline is therefore much less effective in reducing toxicity in epidural block than could be assumed from the official recommendation, which states that a 250 per cent increase in dosage of lignocaine is possible if adrenaline is added. Assuming that 400 mg of plain solution is the maximum dose in conscious patients, then 500 mg would be the maximum if 1:200,000 adrenaline were added.

Apart from the rather disappointing effect of adrenaline in this respect, the toxic effects of adrenaline itself must be considered, especially if accidental intravenous injection is a possibility. This is a rare complication of continuous epidural block (Foldes and Duncalf, 1964).

LIGNOCAIN-DOSIERUNG BEIM EPIDURAL-BLOCK IN BEZUG AUF DIE TOXIZITÄT
ZUSAMMENFASSUNG

POSTGRADUATE COURSE IN ANAESTHESIA

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